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86. **Shunsaku Shiotani and Kemmotsu Mitsuhashi** : Studies on Diazabenzobicyclo[3.3.1]nonane System. V.[*1] Nuclear Magnetic Resonance Spectral Studies on Diazabenzobicyclo[3.3.1]nonane System.

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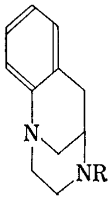
In the previous papers the authors reported the syntheses of five kinds of skeleton belonging to diazabenzobicyclo[3.3.1]nonane system: 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*e*][1,4]diazocine (I)1), 3,4-dihydro-2*H*,6*H*-1,5-methanobenzo[*b*][1,5]diazocine (II)2), 1,2,3,4,5,6-hexahydro-imino-3-benzazocine (III),3,4) 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (IV)3), 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine (V)[*1] and their derivatives.



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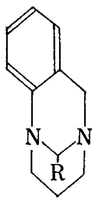
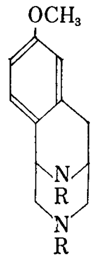
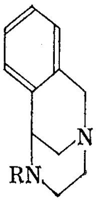


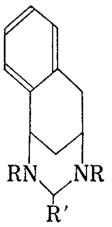
IIa : R=H
IIb : R=C_6H_5



IIIa : R=CH_3



IVa : R=C_2H_5
IVb : R=CH_3



Va : R=C_2H_5, R′=C_6H_5
Vb : R=CH_3 , R′=C_6H_5
Vc : R=C_2H_5, R′=H
Vd : R=CH_3 , R′=H

Chart 1.

In this paper, the authors wish to report the nuclear magnetic resonance spectral supports for the conformation of ring C in the system and the structural elucidations of quarternary ammonium salts of III and IV.

Results and Discussion

Conformation of Ring C in Diazabenzobicyclo[3.3.1]nonane System

The crystallographic analysis of morphine hydrobromide5) has shown its three dimensional structure in which ring D takes a chair form.

In view of the conformational analysis, Eliel in his book6) expressed that both six-membered rings in bicyclo[3.3.1]nonane system and its heterocyclic analogues would take chair conformations if there is no transannular interaction. Similarly, May and his co-workers7) have illustrated the conformation of ring C in benzomorphane system as a chair form.

House, *et al.*8) reported that 3-methyl-3-azabicyclo[3.3.1]nonan-9-one would exist in chair-chair conformation on the basis of the dipolemoment and the nuclear magnetic resonance spectral data, and recently, Lygo, *et al.*9) concluded that the hydrochloride of 3-methyl-3-azabicyclo[3.3.1]nonane exist in chair-chair conformation, while the

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[*1] Part IV. S. Shiotani, K. Mitsuhashi : This Bulletin, **14**, 324 (1966).

[*2] Gofuku, Toyama (塩谷俊作, 三橋監物).

1) S. Shiotani, K. Mitsuhashi : This Bulletin, **12**, 647 (1964).

2) *Idem* : Yakugaku Zasshi, **84**, 656 (1964).

3) *Idem* : *Ibid.*, **84**, 1032 (1964).

4) *Idem* : *Ibid.*, **86**, 169 (1966).

5) M. Mackay, D. C. Hodgkin : J. Chem. Soc., **1955**, 3261.

6) E. L. Eliel : "Stereochemistry of Carbon Compounds", McGraw-Hill Book Company, Inc. New York. p. 295 (1962).

7) S. Saito, E. L. May : J. Org. Chem., **26**, 4536 (1961).

8) H. O. House, P. P. Wickham, H. C. Müller : J. Am. Chem. Soc., **84**, 3139 (1962).

9) R. Lygo, J. McKenna, I. O. Sutherland : Chem. Comm., **1965**, 356.

methiodide of the amine in chair-boat conformation, by the examination of the nuclear magnetic resonance spectra of them.

Under those considerations, the authors also had recognized that ring C in diazabenzobicyclo[3.3.1]nonane system would take a chair form, and detailed, in part II[2] of this series, the nuclear magnetic resonance spectra of 3,4-dihydro-2*H*,6*H*-1,5-methanobenzo[*b*][1,5]diazocine (IIa) and its 11-phenyl- (IIb) and 11-methyl- (IIc) derivatives. However, there was no concrete evidence for the conformation of ring C in diazabenzobicyclo[3.3.1]nonane system, especially in the state of solution. This point has indeed prompted the authors to report the interpretation of the nuclear magnetic resonance spectra of the system.

As shown in Fig. 1 and Table I, the C_3-proton signals of Va (6.48,τ singlet) and Vb (6.67τ, singlet) appeared at higher field than the C_{11}-proton ($H_{IV'}$*3) signal of IIb (4.77 τ, singlet). These differences could be understood in terms of the anisotropic shielding effects of rings A, B and C on the C_3-protons of Va and Vb.

As only two conformations are possible for diazabenzobicyclo[3.3.1]nonane system, a chair form and a boat form of ring C, it may be possible to estimate the magnetic anisotropy effects of rings A, B and C on the C_3-protons and on the C_{11}-protons of the system. The C_3-protons and the C_{11}-protons are designated as illustrated in Fig. 2.

Although it is dangerous to apply the well known McConnell equation[10] and Johnson-Bovey graph[11] for the calculations of the magnetic anisotropy effects of

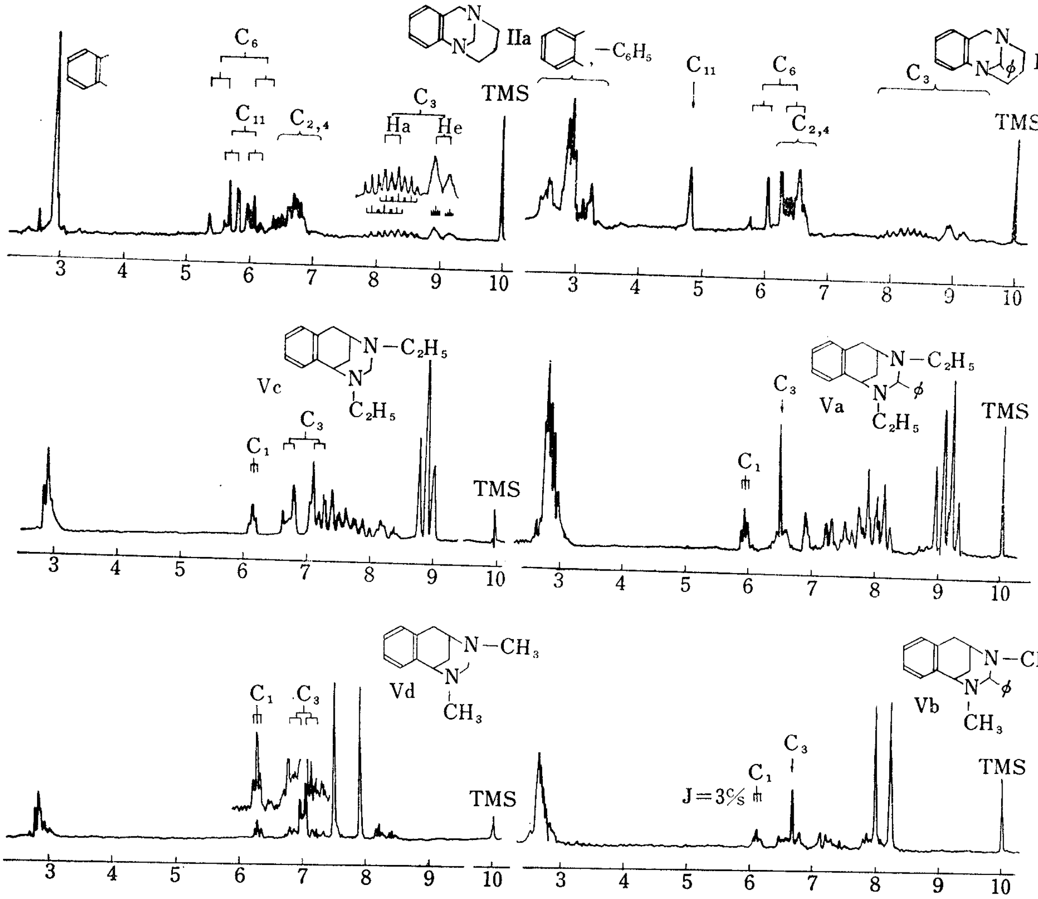

Fig. 1. Nuclear Magnetic Resonance Spectra of IIa and IIb in Deuterochloroform and Va, Vb, Vc and Vd in Tetrachlorocarbon at 60 Mc.

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*3 Assignment of this proton signal was detailed in part II of this series.

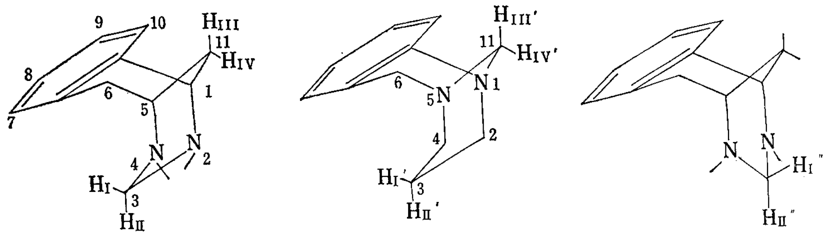
[10] H. M. McConnell: J. Chem. Phys., **27**, 226 (1957).

[11] C. E. Johnson, F. A. Bovey: *Ibid.*, **29**, 1012 (1958).

Table I. Chemical Shifts of Protons (τ)[a]

Compd.	C_3	J	C_{11}	J
IIa[b]	8.26, 9.04 (multiplet)	$J_{3a,3e}=14.5$c.p.s. $J_{3a,2a}\fallingdotseq J_{3a,4a}\fallingdotseq 11.5$c.p.s. $J_{3a,2e}\fallingdotseq J_{3a,4e}=5.5$c.p.s. $J_{3e,2e}\fallingdotseq J_{3e,4e}\fallingdotseq$ $J_{3e,2a}\fallingdotseq J_{3e,4a}=2$–3c.p.s.	5.74, 6.05 (AB-quartet)	J=13c.p.s.
IIb[b]	8.30, 9.04[d] (multiplet)		4.77 (singlet)	
Va[c]	6.48 (singlet)			
Vb[c]	6.67 (singlet)			
Vc[c]	6.70, 7.15 (AB-quartet)	J=10.5c.p.s.		
Vd[c]	6.90, 7.13 (AB-quartet)	J=10c.p.s.		

a) Spectra were determined on solutions in $CDCl_3$ or in CCl_4, using TMS as internal reference by Varian Model A-60 and J.N.M. C-60 spectrometers operated at 60 Mc.
b) $CDCl_3$. *c*) CCl_4. *d*) The splitting pattern is similar to that of IIa.



V II V′

Fig. 2.

diazabenzobicyclo[3.3.1]nonane system without any criticism, it may be valid for the qualitative discussion. Approximately, calculated[*4] values of the effects on $H_{\mathrm{I}} \fallingdotseq H_{\mathrm{I}'}$, $H_{\mathrm{II}} \fallingdotseq H_{\mathrm{II}'}$, $H_{\mathrm{III}} \fallingdotseq H_{\mathrm{III}'}$, $H_{\mathrm{IV}} \fallingdotseq H_{\mathrm{IV}'}$, $H_{\mathrm{I}''}$ and H_{II}'' by the equation and the graph in Dreiding models are as follows: +1.5 p.p.m., −0.3 p.p.m., −0.85 p.p.m., −0.95 p.p.m., −0.95 p.p.m. and −1.0 p.p.m., respectively. The subtractions of the effects, $H_{\mathrm{I}}-H_{\mathrm{IV}'}$, $H_{\mathrm{II}}-H_{\mathrm{IV}'}$, $H_{\mathrm{I}''}-H_{\mathrm{IV}'}$ and $H_{\mathrm{II}''}-H_{\mathrm{IV}'}$ are +2.45 p.p.m., +0.65 p.p.m., 0.0 p.p.m. and −0.05 p.p.m.

Therefore, the observed values, [C_3-proton signal of Va or Vb]—[C_{11}-proton signal (H_{IV}') of IIb]=[1.71 p.p.m. or 1.90 p.p.m.], show that ring C in Va and Vb would exist in chair conformation, and that the C_3-phenyl groups of Va and Vb are equatorial. Similarly, by the fact that C_3-proton signals of Vc (7.15τ (A) and 6.70τ (B), AB-quartet) and Vd (7.13τ (A′) and 6.90τ (B′), AB-quartet) appeared at higher field than the C_{11}-proton signal of IIa (5.74τ and 6.05τ, AB-quartet), it may be concluded that ring C in Vc and Vd would also exist in chair conformation. Consequently, signals A and A′ correspond to H_{I} and B and B′ to H_{II}, but not to $H_{\mathrm{I}''}$ or $H_{\mathrm{II}''}$.

The above conclusion coincides with that obtained by the conformational analysis. Thus, it is assumed that the preferred conformation of ring C in diazabenzobicyclo[3.3.1]nonane system is a chair form.

[*4] Calculations were made by assuming that ($\chi_L-\chi_T$) values of all single bonds are same (-5.5×10^{-30} e.s.u.) and the center of the electric gravity of a bond is at the center of the bond.

In part II[2] of this series, the authors reported that the C_3-H_{ax} ($H_{I'}$) signals of IIa and IIb appeared at lower field than the C_3-H_{eq} ($H_{II'}$) signals by about 0.76 p.p.m. under the influence of the magnetic anisotropy effect of N_1 and N_5.[12] Now, the difference between the observed chemical shifts of H_I and those of H_{II} (0.23~0.45 p.p.m.) may be regarded as the difference in the magnetic anisotropy effects of rings A, B and C on $H_{I'}$ and on $H_{II'}$. Thus, the difference in the magnetic anisotropy effects of the nitrogen atoms (N_1 and N_5) of II between $H_{I'}$ and $H_{II'}$ is estimated to be 0.99~1.21 p.p.m. Using the McConnell equation[11,12] and the data, $r_{H_{ax}-N}$ (2.4A), $r_{H_{eq}-N}$ (3.8A), $\theta_{H_{ax}-N}$ (25°), $\theta_{H_{eq}-N}$ (40°), $\Delta\delta_{N_1,N_5}$ (1.1 p.p.m.), $\Delta\chi_{N_1,N_5}$ is calculated to be 35×10^{-30} e.s.u.

Structural Elucidation of the Quarternary Ammonium Salts of III and IV

Previously, the authors reported[3,4] that 3,11-dimethyl-8-methoxy-1,2,3,4,5,6-hexahydro-imino-3-benzazocine (IIIa) and 2-ethyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo-[*f*][1,4]diazocine (IVa) afforded monomethiodides (IIIa′ and IVa′), respectively, by treating with methyliodide. In this paper the authors report the nuclear magnetic resonance spectral evidences for the determination of the positions of the quarternary nitrogen atoms in IIIa′, IVa′ and 2-methyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine monomethiodide (IVb′).

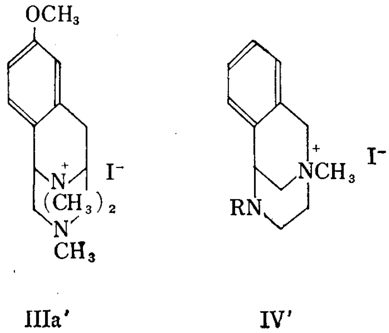
It is well known in the nuclear magnetic resonance studies that the signal of a proton on the carbon atom adjacent to an amine nitrogen atom is remarkably shifted to the lower field by converting the amine to an ammonium salt. As shown in Table II, the C_1-proton signal of IIIa′ was shifted to the lower field by 56 c.p.s. when compared with the corresponding signal of IIIa, whereas the lower field shifts of the methylene proton signals were not so large. These differences suggest that the quarternary ammonium nitrogen atom in IIIa′ is N_{11}, as shown in Fig. 3. In case of IV, the C_6-proton signals of IVa′ and IVb′ appeared at −9 c.p.s. from H_2O signal and at −10 c.p.s. as a broad singlet, while the corresponding signals of IVa and IVb at +33 c.p.s. and +60 c.p.s. as an AB-quartet (J=18 c.p.s.). Furthermore, two N-CH_3 signals of IVb′ appeared at +76 c.p.s. and at +147 c.p.s. These facts support that the quarternary nitrogen atoms of IVa′ and IVb′ are present at 5-position.

Table II. Chemical Shifts of Protons (c.p.s. from H_2O signal)[a]

Compd.	C_1	N-CH_3	O-CH_3
IIIa	+39(t)	+127(s) +136(s)	+31(s)
IIIa′	−17(bs)	+50(s) +73.5(s) +126(s)	+27(s)

Compd.	C_6	N-CH_3
IVa	+33, +60(q)	—
IVb	+33, +60(q)	+161(s)
IVa′	− 9 (s)	+76(s)
IVb′	−10(s)	+76(s) +147(s)

[a] Spectra were determined on solutions in D_2O, using H_2O as internanl reference by Varian Model A-60, J.N.M. C-60 and Hitachi H-60 spectrometers operated at 60 Mc.
(t): triplet. (s): singlet. (bs): broad singlet. (q): AB-quartet.



IIIa′ IV′

Fig. 3.

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[12] S. Yamaguchi, S. Okuda, N. Nakagawa: This Bulletin, **11**, 1465 (1963).

Experimental

2-Methyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (IVb) and Its Monomethiodide (IVb′) 2-(β-Hydroxyethyl)-4-acetamido-1,2,3,4-tetrahydroisoquinoline[3] (1.2 g.) was dissolved in 30% H_2SO_4 (7 ml.) and refluxed for 5 hr. The reaction mixture was made alkaline with 10% NaOH, extracted with $CHCl_3$ and dried over K_2CO_3. After evaporation of $CHCl_3$, the residue was dissolved in ether and treated with HCl gas to afford HCl salt of 2-(β-hydroxyethyl)-4-amino-1,2,3,4-tetrahydroisoquinoline.

A mixture of the HCl salt (0.8 g) and $SOCl_2$ (6 ml.) was allowed to stand overnight at room temperature. After evaporation of the excess of $SOCl_2$, the residue was dissolved in water, washed with benzene, made alkaline with 10% NaOH, extracted with toluene and dried over K_2CO_3.

A mixture of K_2CO_3 (3 g.) and the dried toluene solution was refluxed for about 20 hr. After cooling, the mixture was washed with water and extracted with 10% HCl. The extract was made alkaline with 10 % NaOH, extracted with ether and dried over K_2CO_3. After evaporation of ether, the residue was distilled *in vacuo* to yield 0.3 g. of 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine, b.p. $_{0.4}$ 125~135° (bath temp.), colorless oil.

A mixture of the above amine (244 mg.), formic acid (1.5 ml.) and 35% formalin (1.0 ml.) was heated on a water bath for 1 hr. The reaction mixture was treated as usual to afford IVb, b.p $_{0.3}$ 95~105° (bath temp.), colorless viscous oil. Monomethiodide of IVb was prepared by warming a mixture of IVb (100 mg.) and methyliodide (1 ml.) in MeOH, m.p. 196~201° (decomp.) (from EtOH-AcOEt). *Anal.* Calcd. for $C_{13}H_{19}N_2I \cdot 1/2H_2O$: C, 46.07; H, 5.93; N, 8.26. Found : C, 46.45; H, 5.85; N, 7.82.

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Summary

The interpretation of the nuclear magnetic resonance spectra of some derivatives of 3,4-dihydro-2*H*,6*H*-1,5-methanobenzo[*b*][1,5]diazocine (II) and 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine (V) suggested that ring C in diazabenzobicyclo[3.3.1]nonane system takes a chair form.

The structures of monomethiodides of 3,11-dimethyl-8-methoxy-1,2,3,4,5,6-hexahydro-imino-3-benzazocine (IIIa), 2-ethyl- (IVa) and 2-methyl-1,2,3,4-tetrahydro-1,5-methanobenzo[*f*][1,4]diazocine (IVb) were also determined by the examination of the nuclear magnetic resonance spectra of them.

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